

# ENCODE Data in the UCSC Genome Browser: year 5 update

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## ABSTRACT

The Encyclopedia of DNA Elements (ENCODE), <http://encodeproject.org>, has completed its fifth year of scientific collaboration to create a comprehensive catalog of functional elements in the human genome, and its third year of investigations in the mouse genome. Since the last report in this journal, the ENCODE human data repertoire has grown by 898 new experiments (totaling 2886), accompanied by a major integrative analysis. In the mouse genome, results from 404 new experiments became available this year, increasing the total to 583, collected during the course of the project. The University of California, Santa Cruz, makes this data available on the public Genome Browser <http://genome.ucsc.edu> for visual browsing and data mining. Download of raw and processed data files are all supported. The ENCODE portal provides specialized tools and information about the ENCODE data sets.

## INTRODUCTION

The mission and scope of the Encyclopedia of DNA Elements (ENCODE) Project is well described in previous publications by the ENCODE Consortium (1–2), and results from coordinated analysis of ENCODE results (3) are also available. Previous manuscripts in this publication (4–6) have described the project's progress since 2007 and detailed how the ENCODE Data Coordination Center at the University

of California, Santa Cruz, (UCSC) has worked with ENCODE laboratories worldwide to import its production data, supporting documentation and metadata, and has made the data accessible to the broader biomedical community. A companion article in this issue, ‘The UCSC Genome Browser database: Extensions and updates 2013’, provides background information about the UCSC Genome Browser database and infrastructure (7–8) that underlies ENCODE support at UCSC. This article focuses on ENCODE data and access tools introduced during 2012, the fifth and final year of the initial whole-genome production phase of the project.

## DATA AVAILABILITY

All ENCODE production data for the 5-year initial production phase of the project have now been submitted to the ENCODE Data Coordination Center at UCSC. UCSC has performed quality review and publicly released all conforming ENCODE data sets along with metadata, as both tracks for browsing and downloadable files for data mining. In the human genome, 288 cell and tissue types are now represented, covering 32 assays. Chromatin features and sites of DNA binding are mapped for >300 factors and marks. In mouse, 81 cell and tissue types were surveyed in five experimental assays.

### Human genome

The results of five new experiment types were released during the fifth year: chromatin interactions based on chromosome conformation capture carbon copy (5C) and chromatin interaction analysis by paired-end tag sequencing (ChIA-PET) methods, proteogenomics and

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DNA replication timing by both sequencing and microarray methods.

Although DNA is a linear molecule, it is packed and organized inside the nucleus in a 3D milieu, and gene regulation can be affected by interactions from elements located hundreds of kilobases distant in the genome. Long-range chromatin looping interactions can be detected using various techniques, including chromosome conformation capture (9) and chromatin interaction analysis with paired-end tag (10). The ENCODE chromatin interactions data sets comprise experiments in 14 cell types.

Proteogenomic methods differ from conventional mass spectrometry proteomic methods that identify peptides by comparing them with peptides produced from known proteins. In contrast, proteogenomic methods compare peptides with all peptides that might be produced by the six translation frames of the genome to identify the genomic region from which the peptides were produced. Study of proteogenomic data offers insights into regulatory mechanisms, including translation, pre-messenger RNA (mRNA) splicing and transcript diversity, nonsense-mediated decay and transcription of novel protein-coding genes. The ENCODE proteogenomics data are available in four cell types. Figure 1 presents a Genome Browser session that includes proteogenomics data in conjunction with ENCODE gene, transcriptome and regulatory data sets.

The order in which DNA is duplicated during the synthesis phase of the cell cycle is correlated with the expression of genes and the structure of chromosomes; replication timing is known to be an important feature for epigenetic control of gene expression. ENCODE 'Repli-chip' (microarray) experiments are available in 9 cell types, and 'Repli-seq' (sequencing) experiments in 15.

The encyclopædia of genes and gene variants (GENCODE) gene set (11) is a fundamental resource produced by ENCODE, providing high-quality manual annotation from the Human and Vertebrate Analysis and Annotation (HAVANA) group merged with evidence-based automated annotation from Ensembl (12) across the human genome. For the final release (V12), the data organization and display were improved to make the data more accessible and intuitive. Annotations are now categorized according to their function and level of support. Color coding reflects non-coding, coding, pseudogene or problem status. To complement the 'Comprehensive' gene set, a new 'Basic' subset provides a simplified view intended for the majority of users, by filtering incomplete and problem annotations while still ensuring that at least one annotation is displayed at every locus. For researchers who require more detail regarding the degree of evidence supporting individual coding transcripts, a five-level scoring metric is provided, based on assessment of alignments of mRNAs and expressed sequence tags (ESTs) across the full length of the annotation. Filtering options allow tuning of the display based on the basic biological function of the transcript (coding, non-coding, etc.), annotation method (manual versus automated) or specific biotype characterization ([http://www.gencodegenes.org/gencode\\_biotypes.html](http://www.gencodegenes.org/gencode_biotypes.html)). Finally, two additional annotation subtracks are provided: the '2-Way Pseudogene' subtrack shows

consensus pseudogenes predicted by two pipelines [Yale Pseudopipe (13) and UCSC Retrofinder (14)], and the 'PolyA' subtrack presents polyA signals and sites manually annotated on the genome based on transcribed evidence.

The majority of ENCODE primary data submitted and released in the past year for the human genome expanded the existing tracks with additional experiments; cell types, subcellular fractions, transcription factors or histone marks were also mapped. The total complement of data sets available is summarized in Tables 1 and 2. All links mentioned in this publication are collected in Table 3.

Much of the primary human data (January 2011 data freeze) has been processed uniformly and used as the basis of the September 2012 published integrated analyses performed by the ENCODE analysis group. Results from this processing and analysis are accessible in the UCSC browser via a UCSC public Track Data Hub (ENCODE Analysis Hub) accessed at <http://genome.ucsc.edu/cgi-bin/hgHubConnect>. All data have been reprocessed using the ENCODE uniform processing pipeline, including signal tracks corrected for read length and mappability (<http://code.google.com/p/align2rawsignal>), peak calls from the SPP (15) and PeakSeq (16) peak callers filtered using the irreproducible discovery rate (17), computed RNA contigs from seven cellular localizations (18) and genome segmentations for the six Tier 1 and 2 cell lines. A total of 2876 data sets are included in the hub, with a reduced set displayed by default. The track organization for the analysis hub is illustrated in Figure 2. Additional background and resources related to the ENCODE analysis effort are provided on the portal's Integrative Analysis page, described later.

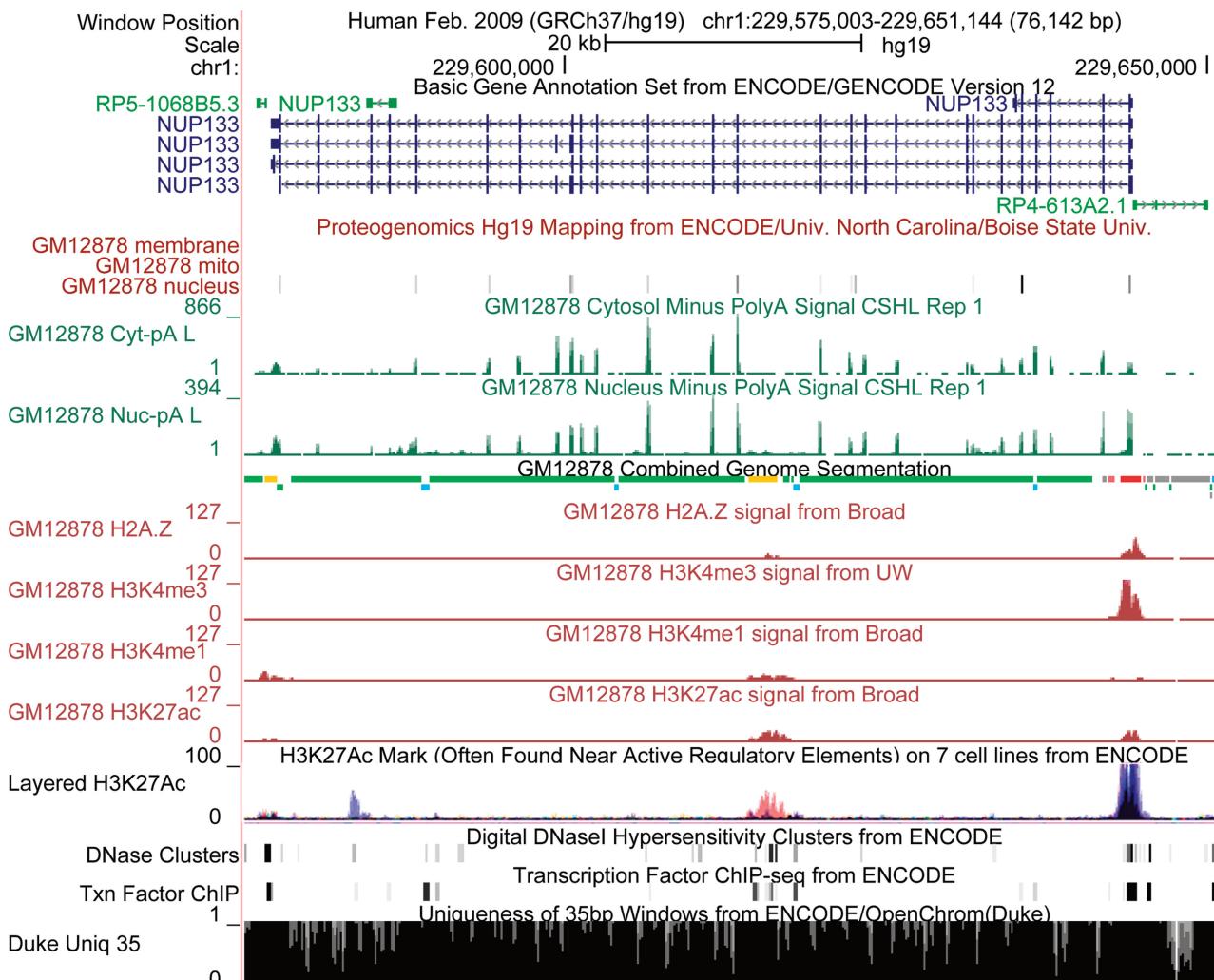
## Mouse genome

Although the ENCODE project aims to discover all DNA sequences in the human genome with biochemical function under the expectation that these will likely be functional, extending the analysis to use comparative genomics approaches was identified as a fruitful direction for the project. Thus, in the third year, a Mouse ENCODE Project was inaugurated (19). Assays identical to those being used in the ENCODE project are performed in cell types in mouse that are similar or homologous to those studied in the human project. The comparison will be used to discover which epigenetic features are conserved between mice and humans.

The past year marked the expansion of the UCSC Mouse browser (mm9/NCBI37) from a few preliminary ENCODE tracks to a full representation of Mouse ENCODE data production. A total of 20 tracks of ChIP-seq, RNA-seq and DNase-seq were released, reflecting 583 experiments. Figure 3 provides a graphical view of the Mouse ENCODE data availability.

## Data distribution

The ENCODE Data Coordination Center at UCSC (DCC) has accessioned all relevant ENCODE data at the Gene Expression Omnibus (GEO) (20) and the Short Read Archive. Since September 2011, the DCC has archived



**Figure 1.** ENCODE data displayed in the UCSC Genome Browser together with annotations from the ENCODE Analysis Hub in the region of the nucleoporin gene NUP133 demonstrate the power this diversity of data provides for visual interpretation. The GENCODE Basic gene set shows this gene having four protein-coding splice variants and three smaller non-coding transcripts nearby. The proteogenomics track shows support for many of the coding exons, with protein localized in the nucleus, but not in plasma membrane or mitochondria. The long polyA RNA signal shows strong peaks over the exons and low intron signal in the cytosol, with greater signal in the nucleus. This is expected because nuclear mRNAs are not all completely spliced. The Combined Genome Segmentation integrates signal from many histones and classifies regions into those with characteristics of promoters (red), enhancers (yellow), insulators (blue), transcribed regions (green) and repressed (gray). Below are signal tracks from four of the eight histone modifications used as input to the segmentation. The promoter and transcribed regions agree with the RNA evidence, and like the RNA evidence show no evidence of transcription of the non-coding gene to the right of NUP133. Underneath the GM12878 histone signals is a track that overlays one of the histone signals, H3K27Ac, in seven different cell lines (with GM12878 shown in red). A peak in H3K27Ac appears at the enhancer, but as is often the case with enhancers, this appears to be relatively cell specific in contrast to the larger peak near the promoter, where the black coloration indicates the peak is shared by many cell types. The DNase hypersensitivity and transcription factor tracks also provide evidence for both promoter and enhancer. Finally the mappability track indicates regions where short reads are not uniquely mappable, indicating the data are incomplete and therefore harder to interpret. Although most of this region is mappable, there are many small regions throughout and one larger region on the right where mapping is problematic. Overall, the ENCODE data in this region show strong evidence that this is a nuclear-localized protein-coding gene with a promoter that is used in a wide variety of cell types, and is likely to be regulated by tissue-specific enhancers as well.

a total of 3346 GEO Samples across 53 GEO Series for humans (GRCh37/hg19) and mice (NCBI37/mm9). ENCODE data now encompasses a total of 4835 GEO Samples and 98 GEO Series. ENCODE GEO submissions are listed on the GEO ENCODE summary page, <http://www.ncbi.nlm.nih.gov/geo/info/ENCODE.html>. ENCODE has been assigned National Center for Biotechnology Information (NCBI) BioProject identifiers to further organize the data: PRJNA30707 for Human ENCODE (with the subproject PRJNA63443 for production phase

data) and PRJNA50617 for Mouse ENCODE. Data in each project are further categorized as ‘epigenomic’, ‘functional genomics’ or ‘transcriptome’. Both UCSC and GEO are archival sites for 2007–12 ENCODE data, and user choice of repository is largely a matter of preferred interface.

All released data from ENCODE are tagged with permanent DCC accessions. Each accession represents a logical experiment, and therefore groups-related files representing different levels of results (e.g. sequence files, Binary Alignment/Map (BAM) alignments, signal graphs

**Table 1.** The full complement of ENCODE data sets summarized by cell type [types annotated as cancer are marked with asterisk (\*)]

Cell type	Tissue	Description	Data sets			
			TF/His	RNA	Other	Total
Tier 1 initial						
GM12878	Blood	Lymphoblastoid	137	27	49	213
K562*	Blood	Leukemia	247	45	80	372
Tier 1 added in 2011						
H1-hESC	Embryonic stem	Embryonic stem	96	14	23	133
Tier 2 initial						
HeLa-S3*	Uterine cervix	Cervical carcinoma	93	14	30	137
HepG2*	Liver	Liver carcinoma	118	19	26	163
HUVEC	Umbilical endothelium	Umbilical vein endothelial	37	13	16	66
Tier 2 added in 2011						
A549*	Lung	Lung carcinoma	89	22	12	123
CD14+	Blood	Monocyte	17	4	4	25
IMR90	Lung	Lung fibroblast	11	16	10	37
MCF-7*	Breast	Breast carcinoma	50	15	32	97
SK-N-SH*	Brain	Neuroblastoma	36	16	7	59
Tier 2 added in 2012						
CD20+	Blood	B cell	11	5	4	20
H1-neuron	Neuron	H1ES-derived neuron	5	3	1	9
LHCN-M2	Muscle	Myoblast	7	2	4	13
Human: totals						
Tier1 + Tier2 (14)			954	215	298	1467
Tier 3 (274)			591	94	734	1419
All (288)			1545	309	1032	2886
Mouse						
All (81)			381	102	100	583

Studies in the human genome focused on common cell types in designated ‘tiers’, with Tier1 most intensively studied, followed by Tier 2. A total of 10 292 files have been released referenced to the human (hg19/GRCh37) genome. For mouse (mm9/NCB37), the comparable number is 8952 files. Data are available for download from the UCSC download server; for access see <http://encodeproject.org/ENCODE/downloads.html> and <http://encodeproject.org/ENCODE/downloadsMouse.html>. File formats are described on the ENCODE Portal File Formats page.

and peaks) for multiple replicates. ENCODE data sets at UCSC include GEO accessions in the accessible metadata.

## ACCESS TOOLS AND FEATURES

A key focus of the past year has been to make the breadth of ENCODE data more readily visible and accessible. Specifically, UCSC has provided new web tools for locating and selecting data of interest, expanded the web portal to include new resources that aid in the interpretation of ENCODE data and developed new tutorial and outreach materials.

### Experiment Matrix web tools

The ‘Experiment Matrix’ tool on the ENCODE portal is a set of three web pages that provide an up-to-date view of the breadth of ENCODE data available, along with an interface for selecting experiments for viewing in the browser or downloading as files for analysis. The main Experiment Matrix page shows the number of experiments for each cell type/assay pairing. The ChIP-seq Experiment Matrix page provides a view of the transcription factor and histone modification data sets, showing experiments by cell type and antibody target. The Experiment Summary page lists the number of experiments by assay type alone and includes annotations that are cell type independent (annotations on the reference genome). Each page has a file/track selector. Clicking an experiment

item produces a search window listing the resulting files or tracks listed. Details about a file, including GEO accessions, are viewed from the search results listing by clicking the down arrow glyph next to the file of interest. An ‘Overview’ link provides help. Experiment Matrix tools are available for both human and mouse (Figure 3) data. The experiment collections presented in matrix form are also available in list form, with downloads provided in Comma Separated Value (CSV) and Excel (XLS) formats via the ‘Experiment List’ pages on the ENCODE portal.

### Portal resources

#### Integrative analysis

The completion of a comprehensive and coordinated integrative analysis of human ENCODE data by the consortium analysis group resulted in numerous resources published in September 2012, described at <http://encodeproject.org/ENCODE/analysis.html>. Key resources include a publications package of 30 articles with coordinated publication in three journals, a Nature ‘microsite’ and a virtual machine analysis platform with access to code bundles allowing user replication of the ENCODE analysis results.

#### Quality metrics

The ENCODE Consortium analysis working group has devoted considerable resources to analyzing the quality

**Table 2.** The full complement of ENCODE data sets summarized by assay

Data type/assay	Experiments
Chromatin interactions	
5C	14
ChIA-PET	8
DNA methylation	
Methyl array	125
Methyl RRBS	95
Methyl-seq	20
Histone modifications	
ChIP-seq	315
ChIP-seq (MOUSE)	179
Open chromatin	
DNase-DGF	56
DNase-DGF (MOUSE)	22
DNase-seq	221
Dnase-seq (MOUSE)	55
FAIRE-seq	39
RNA profiling	
CAGE	78
Exon array	158
RNA-chip	26
RNA-PET	31
RNA-seq	245
RNA-seq (MOUSE)	102
Transcription factor binding sites	
ChIP-seq	1229
ChIP-seq (MOUSE)	202
Other	
DNA cleavage	1
DNA-PET	6
GENCODE genes	7
Genotype	64
Negative regulatory elements	2
Nucleosome positioning	2
Proteogenomics	14
Replication timing	24
Replication timing (MOUSE)	18
RNA binding proteins	47
Short read mapability	13
Short read mapability (MOUSE)	5

Descriptive overviews along with methods and references are included in the description page that accompanies all data sets.

of the data produced using a variety of metrics. The resulting quality metrics are available from the ENCODE portal (<http://encodeproject.org/ENCODE/qualityMetrics.html>). The Quality Metrics page displays downloadable spreadsheets showing quality metrics for human ENCODE data sets, along with descriptions of the metrics and what they appear to measure. Data set metrics are included for DNase I hypersensitive sites sequencing (DNase-seq), formaldehyde-assisted isolation of regulatory elements sequencing (FAIRE-seq), chromatin immunoprecipitation sequencing of transcription factor binding sites (TFBS ChIP-seq), Histone ChIP-seq and ChIP Controls. The software used to generate the quality metrics is described on the Software Tools page of the ENCODE portal.

### Software tools

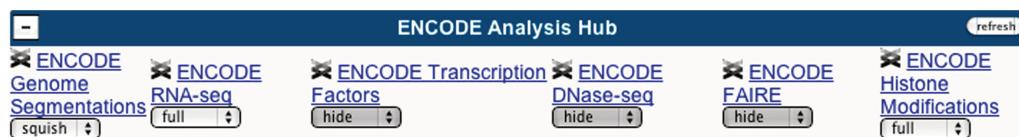
A significant product of the ENCODE project has been the evaluation and development of software to process and analyze the data sets (largely high-throughput sequencing). This section of the portal <http://encodeproject.org/ENCODE/softwareTools.html> provides descriptions and references for 22 software packages used to create the primary data sets generated by the ENCODE production laboratories and the downstream analyses of the ENCODE analysis group. These include peak callers [e.g. model-based analysis of ChIP-Seq (MACS) (21), SPP (15) and PeakSeq (16)], signal generators (e.g. Wiggle), multi-data type integration tools [e.g. Segway (22) and ChromHMM (23)] and quality assessment tools [e.g. irreproducible discovery rate (17)]. A companion page <http://encodeproject.org/ENCODE/analysisTools.html> describes and references seven additional tools of interest to users who are analyzing and using ENCODE data in their own research [e.g. Factorbook (24)].

### Data standards: experiment guidelines

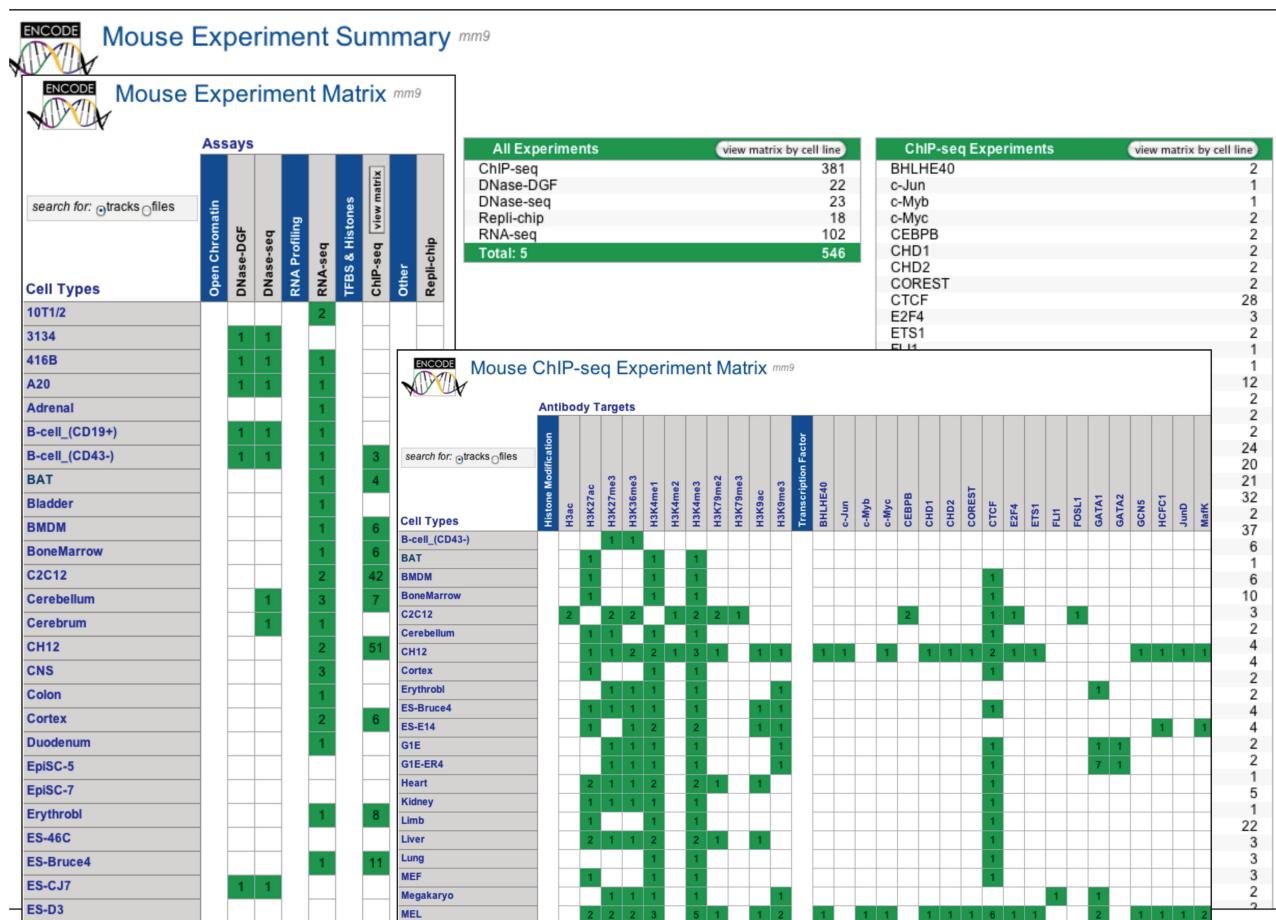
A notable product of the ENCODE project has been the definition of guidelines for conducting and reporting

**Table 3.** All links mentioned in this publication are collected in this table

ENCODE: <a href="http://encodeproject.org">http://encodeproject.org</a>
Genome Browser: <a href="http://genome.ucsc.edu">http://genome.ucsc.edu</a>
Five-level scoring metric filtering options: <a href="http://www.gencodegenes.org/gencode_biotypes.html">http://www.gencodegenes.org/gencode_biotypes.html</a>
UCSC download server (human): <a href="http://encodeproject.org/ENCODE/downloads.html">http://encodeproject.org/ENCODE/downloads.html</a>
UCSC download server (mouse): <a href="http://encodeproject.org/ENCODE/downloadsMouse.html">http://encodeproject.org/ENCODE/downloadsMouse.html</a>
ENCODE Analysis Hub: <a href="http://genome.ucsc.edu/cgi-bin/hgHubConnect">http://genome.ucsc.edu/cgi-bin/hgHubConnect</a>
ENCODE uniform processing pipeline: <a href="http://code.google.com/p/align2rawsignal">http://code.google.com/p/align2rawsignal</a>
GEO ENCODE summary page: <a href="http://www.ncbi.nlm.nih.gov/geo/info/ENCODE.html">http://www.ncbi.nlm.nih.gov/geo/info/ENCODE.html</a>
Integrative Analysis of ENCODE data: <a href="http://encodeproject.org/ENCODE/analysis.html">http://encodeproject.org/ENCODE/analysis.html</a>
ENCODE portal: Quality Metrics: <a href="http://encodeproject.org/ENCODE/qualityMetrics.html">http://encodeproject.org/ENCODE/qualityMetrics.html</a>
ENCODE portal: Software tools: <a href="http://encodeproject.org/ENCODE/softwareTools.html">http://encodeproject.org/ENCODE/softwareTools.html</a>
ENCODE portal: Analysis tools: <a href="http://encodeproject.org/ENCODE/analysisTools.html">http://encodeproject.org/ENCODE/analysisTools.html</a>
ENCODE portal: platform characterization: <a href="http://encodeproject.org/ENCODE/platform_characterization.html">http://encodeproject.org/ENCODE/platform_characterization.html</a>
ENCODE portal: publications: <a href="http://encodeproject.org/ENCODE/pubs.html">http://encodeproject.org/ENCODE/pubs.html</a>
ENCODE file formats: <a href="http://genome.ucsc.edu/FAQ/FAQformat.html#ENCODE">http://genome.ucsc.edu/FAQ/FAQformat.html#ENCODE</a>
Tutorial and training materials by OpenHelix: <a href="http://openhelix.com/ENCODE2">http://openhelix.com/ENCODE2</a>
Introductory tutorial: <a href="http://openhelix.com/ENCODE">http://openhelix.com/ENCODE</a>
OpenHelix QRC: <a href="http://www.openhelix.com/cgi/qrcOrder.cgi">http://www.openhelix.com/cgi/qrcOrder.cgi</a>
ENCODE announcement list: <a href="https://groups.google.com/a/soe.ucsc.edu/forum/#!forum/encode-announce">https://groups.google.com/a/soe.ucsc.edu/forum/#!forum/encode-announce</a>



**Figure 2.** The ENCODE Analysis Hub at the EBI hosts over 2800 ENCODE data sets, organized in six tracks controlled via the track menu shown here.



**Figure 3.** All three screens of the Experiment Matrix for mouse are shown overlaid. The Data Summary screen lists experiments by data type, and provides launching to the two matrix screens that organize the data by assay and cell type. Clicking the appropriate table row or matrix cell launches a Track or File search tool (based on the Track/File selector control) that allows further refinement of the selection for browsing or download.

functional genomics experiments performed using high-throughput sequencing technologies. Guidelines and ‘Best Practices’ developed by the ENCODE project for ChIP-seq (25), RNA-seq, DNase-seq, FAIRE-seq and DNA methylation, along with cell culture guidelines, are available from this page.

#### Data standards: platform characterization

This new portal page ([http://encodeproject.org/ENCODE/platform\\_characterization.html](http://encodeproject.org/ENCODE/platform_characterization.html)) provides summary descriptions and references to studies that illuminate the research technologies underpinning the ENCODE resource. Factors affecting ChIP-seq and RNA-seq experimentation are highlighted, and provide valuable aid to interpretation of the data.

#### Publications

The Publications page, <http://encodeproject.org/ENCODE/pubs.html> was extensively expanded this year to comprise a comprehensive list of 150 publications covering methods, resources and biological findings produced by the ENCODE Consortium and from ENCODE-funded projects. A subsidiary page has references to 111 publications based on ENCODE data that were written by authors outside the consortium.

#### Tutorial and outreach materials

A second more detailed tutorial on accessing ENCODE data was developed this year and is available from <http://openhelix.com/ENCODE2>. The original introductory

tutorial remains available at <http://openhelix.com/ENCODE>. OpenHelix also offers a Quick Reference Card. The Quick Reference Card gives an overview of the site and the numerous methods to access and view ENCODE data within the UCSC Genome Browser using screen shots and callouts to highlight the various features and functions. Cards may be ordered at <http://www.openhelix.com/cgi/qrcOrder.cgi>.

## FUTURE WORK

Although the main production coordination of data for the next phase of ENCODE will be coordinated and managed by Stanford, UCSC will continue to provide data hosting and access tools for current and future ENCODE data. UCSC will incorporate integrated and ‘best-of-breed’ ENCODE data sets from this phase into the UCSC Genome Browser database. An update of the ‘ENCODE Regulation’ track set to incorporate newer data is in progress, and a companion track set is planned for the Mouse genome. Although the bulk of the primary data from the next phase of ENCODE will not be imported into the UCSC browser database and thus will not be available as native tracks, UCSC will provide download access to the data, and visualization via the Browser’s Track Data Hub feature.

## CONTACT INFORMATION

General questions and feedback about ENCODE data at UCSC should be directed to the UCSC browser mailing list: [genome@soe.ucsc.edu](mailto:genome@soe.ucsc.edu). Specific questions about details of laboratory methods or data interpretation should be directed to the ENCODE laboratory contact listed on the description page for that data set. We announce releases of new ENCODE data via the ENCODE announcement list. To subscribe, visit <https://groups.google.com/a/soe.ucsc.edu/forum/#forum/encode-announce>.

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